Influence of Antituberculosis Drug Resistance and *Mycobacterium tuberculosis* Lineage on Outcome in HIV-Associated Tuberculous Meningitis


HIV-associated tuberculous meningitis (TBM) has high mortality. Aside from the devastating impact of multidrug resistance (MDR) on survival, little is understood about the influence of other bacterial factors on outcome. This study examined the influence of *Mycobacterium tuberculosis* drug resistance, bacterial lineage, and host vaccination status on outcome in patients with HIV-associated TBM. *Mycobacterium tuberculosis* isolates from the cerebrospinal fluid of 186 patients enrolled in two studies of HIV-associated TBM in Ho Chi Minh City, Vietnam, were tested for resistance to first-line antituberculosis drugs. Lineage genotyping was available for 122 patients. The influence of antituberculosis drug resistance and *M. tuberculosis* lineage on 9-month mortality was analyzed using Kaplan-Meier survival analysis and Cox multiple regression models. Isoniazid (INH) resistance without rifampin resistance was associated with increased mortality (adjusted hazard ratio [HR], 1.78, 95% confidence interval [CI], 1.18 to 2.66; *P* = 0.005), and multidrug resistance was uniformly fatal (*n* = 8/8; adjusted HR, 5.21, 95% CI, 2.38 to 11.42; *P* < 0.0001). The hazard ratio for INH-resistant cases was greatest during the continuation phase of treatment (after 3 months; HR, 5.05 [95% CI, 2.23 to 11.44]; *P* = 0.0001). Among drug-susceptible cases, patients infected with the “modern” Beijing lineage strains had lower mortality than patients infected with the “ancient” Indo-Oceanic lineage (HR, 0.29 [95% CI, 0.14 to 0.61]; *P* = 0.001). Isoniazid resistance, multidrug resistance, and *M. tuberculosis* lineage are important determinants of mortality in patients with HIV-associated TBM. Interventions which target these factors may help reduce the unacceptably high mortality in patients with TBM.

Tuberculous meningitis (TBM) is the most severe form of disease caused by *Mycobacterium tuberculosis*. Outcomes are extremely poor, with mortality in HIV-uninfected patients of approximately 30% and severe neurological sequelae in up to half of those surviving (21, 25). HIV-infected individuals are more susceptible to developing the severe disseminated forms of tuberculosis (TB), and mortality in these patients can exceed 60% (11, 22). The best current predictor of clinical outcome is the British Medical Research Council (MRC) disease stage at which a patient is diagnosed and when the patient starts appropriate chemotherapy (6). Little is known about the influence of other factors on outcome, including antituberculosis drug resistance, pathogen lineage, and *Mycobacterium tuberculosis* bacillus Calmette-Guérin (BCG) vaccination status. A better understanding of these complex interactions will aid in developing improved antituberculosis regimens or adjuvant therapies for TB.

Optimal antibiotic treatment regimens for TB have never been determined in adequately powered randomized controlled trials, and existing recommendations have been extrapolated from the evidence of trials for pulmonary TB. A randomized controlled trial comparing standard treatment with additional levofloxacin and high-dose rifampin is currently recruiting subjects at our center (8). Adjunctive dexamethasone reduces mortality (21).

The prevalence of drug-resistant strains of *M. tuberculosis* is increasing globally, and the World Health Organization (WHO) estimates that 7.4% of tuberculosis cases globally are resistant to isoniazid (INH) and 3.3% are multidrug resistant (MDR; defined as resistance to at least isoniazid and rifampin) (26). In Ho Chi Minh City, 25% of new smear-positive patients have INH-resistant TB and 3.8% have MDR-TB (16). In resource-limited high-TB-burden settings, drug-resistant TB is rarely diagnosed within a clinically useful time frame, owing to the difficulty of isolating organisms from the paucibacillary cerebrospinal fluid (CSF), the lack of laboratory capacity for *M. tuberculosis* culture, and the slow growth of the organism. MDR-TBM is almost universally fatal in the developing world (2, 20), but there are few data regarding the impact of other forms of drug resistance on outcome.

In view of the poor CSF penetration of most first-line antituberculosis drugs, the optimal treatment for TBM may require different drug combinations or dosages than those for pulmonary disease. Only INH and pyrazinamide (PZA) penetrate the blood-brain barrier well, while rifampin (RIF), streptomycin (SM), and ethambutol (EMB) penetrate poorly (5). RIF concentrations in the CSF rarely exceed the MIC for mycobacteria, and in plasma the majority (80%) of RIF is protein bound, although the significance of this is unclear (5). It is probable that RIF and INH, the two key...
drugs used for the treatment of pulmonary TB, are also crucial for treatment of TBM. This is supported by the high mortality rate in patients with MDR-TBM receiving standard first-line treatment regimens (15). Thus, examination of the impact of different drug resistance patterns on response to therapy, in combination with pharmacokinetic/pharmacodynamic studies of CSF drug penetration, will help inform rational choices from among current treatment options and the design of trials of novel agents.

A previous pilot study from Vietnam suggested that, while mortality for patients with MDR-TBM was 100%, patients infected with an INH-resistant RIF-susceptible isolate did not have significantly worse outcomes than those infected with fully susceptible organisms, despite the observation that INH resistance prolonged bacterial clearance from the CSF (20). However, the number of patients in this study may have been too small to detect an impact. A recent retrospective analysis of 1,896 TBM cases in the United States found a significant association between INH resistance and mortality (odds ratio [OR], 2.07; 95% confidence interval [CI], 1.30 to 3.29) (25).

The aim of this study was to examine the effects of antituberculosis drug resistance and M. tuberculosis lineage on outcome in patients with HIV-associated TBM.

MATERIALS AND METHODS

Patients enrolled into two consecutive studies of HIV-associated TBM who had M. tuberculosis isolated from the CSF were included in the analysis. The first study was an observational cohort study of 58 HIV-associated TBM patients admitted to the Hospital for Tropical Diseases, Ho Chi Minh City (HCMC), between November 2004 and September 2005 (22). The second study was a randomized controlled trial (RCT) of antiretroviral therapy (ART) initiation in HIV-associated TBM (23). Briefly, 253 HIV-infected antiretroviral agent-naïve TBM patients were randomly assigned to receive immediate or deferred (2 months) initiation of ART between September 2005 and December 2008. The trial was conducted at two sites in HCMC: Pham Ngoc Thach Hospital (PNT) and the Hospital for Tropical Diseases (HTD). Both studies were approved by the Oxford Tropical Research Ethics Committee, the institutional review boards of the participating hospitals, and the Health Services of HCMC.

All participants were treated with standard first-line antituberculosis chemotherapy according to the Vietnamese National TB Programme guidelines: isoniazid (5 mg/kg of body weight), rifampin (10 mg/kg), pyrazinamide (25 mg/kg), and ethambutol (20 mg/kg) once daily for 3 months, followed by a continuation phase of isoniazid and rifampin for 6 months. Intramuscular streptomycin (20 mg/kg) was added for patients previously treated for tuberculosis or for those in whom drug resistance was suspected due to clinical deterioration. All patients were treated with adjunctive dexamethasone (21).

The antiretroviral regimen consisted of zidovudine (300 mg, twice daily), lamivudine (150 mg, twice daily), and efavirenz (800 mg, once daily). Antiretroviral treatment was not generally available in Vietnam at the time of the observational study, and therefore only 7/58 patients in this study received antiretroviral therapy.

Isolates of M. tuberculosis were tested by the 1% proportion method for susceptibility to INH (0.2 µg/ml), RIF (40 µg/ml), SM (4 µg/ml), EMB (2 µg/ml), and PZA (200 µg/ml) at the microbiology laboratory of PNT. Drug susceptibility results were not available in time to influence antituberculosis treatment.

M. tuberculosis isolates were archived for long-term storage and therefore available for lineage genotyping at only one hospital site (HTD). Isolates were typed by large-sequence polymorphism (LSP) typing (3). Isolates were grouped into the 3 major lineages found in Vietnam: Indo-Oceanic, Euro-American, and East-Asian/Beijing.

Statistical analysis. We visualized survival by antituberculosis drug resistance group or M. tuberculosis lineage by using Kaplan-Meier curves.

RESULTS

The primary analysis of the observational cohort study and the randomized controlled trial have been previously reported (22, 23). We included all patients from these studies who had M. tuberculosis isolated from the CSF and available for analysis of drug resistance: 46/58 (79%) from the cohort study and 141/253 (56%) from the RCT. We further excluded one duplicate patient from the cohort study who was subsequently enrolled into the randomized trial, leading to a total sample size of 186 patients. Baseline characteristics of these patients are reported in Table 1. Of the included 186 patients, 112 patients died during the 9 months of follow-up of the study and 55 survived; the remaining 19 patients were lost to follow-up and censored at the time they were last known to be alive. The overall 9-month mortality in the study was significantly worse than those infected with fully susceptible isolates (20). However, the number of patients in this study may have been too small to detect an impact. A recent retrospective analysis of 1,896 TBM cases in the United States found a significant association between INH resistance and mortality (odds ratio [OR], 2.07; 95% confidence interval [CI], 1.30 to 3.29) (25).

Comparison of resistance was based on three prospectively defined resistance groups: fully susceptible or SM monoresistance; INH resistance with or without SM resistance; multidrug resistance (MDR). To determine whether ignoring SM resistance in the grouping was consistent with the study data, we tested whether adding an indicator for SM resistance to the multiple Cox regression model described below produced a significant effect. In addition, we compared the three groups with a Cox regression model with indicator variables for the different resistance groups and adjustment for MRC TBM stage at presentation, (log-transformed) CD4 cell count, and the cohort group (observational cohort study, RCT with immediate ART, RCT with deferred ART). The proportional hazards assumption of the Cox regression was tested based on scaled Schoenfeld residuals. If it was violated for a covariate, alternatively we fit separate (time-dependent) regression coefficients for the intensive TB treatment phase (first 3 months) and thereafter.

Analyses were performed both with and without inclusion of patients receiving streptomycin treatment. CD4 cell counts were missing for 18 subjects, and the TBM grade for 1 patient of the 186 participants included in the analysis and the adjusted Cox regression analyses were based on multiple imputation of missing covariates.

All statistical analyses were performed with the statistical software R version 2.11.1 (17) and the companion R package Mice 2.8 (24).

### Table 1: Baseline characteristics of the 186 patients with a CSF culture for M. tuberculosis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Prospective descriptive study (n = 45)</th>
<th>Immediate ART (n = 77)</th>
<th>Deferred ART (n = 64)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, in yrs (IQR)</td>
<td>27 (23–31)</td>
<td>28 (25–34)</td>
<td>29 (25–33)</td>
</tr>
<tr>
<td>No. (%) males</td>
<td>41 (91.1)</td>
<td>71 (92.2)</td>
<td>57 (89.1)</td>
</tr>
<tr>
<td>Median wt, in kg (IQR)</td>
<td>50 (45–51)</td>
<td>45 (40–51)</td>
<td>46 (40–50)</td>
</tr>
<tr>
<td>No. (%) with previous tuberculosis/total evaluated</td>
<td>8/42 (19.1)</td>
<td>8/76 (10.5)</td>
<td>6/63 (9.5)</td>
</tr>
<tr>
<td>Median CD4 T-lymphocyte count, in cells/µl (IQR)</td>
<td>32 (12–59)</td>
<td>28 (16–108)</td>
<td>32 (14–78)</td>
</tr>
<tr>
<td>No. (%) with CSF positive by Ziehl-Neelsen stain</td>
<td>32 (71.1)</td>
<td>38 (49.4)</td>
<td>37 (57.8)</td>
</tr>
</tbody>
</table>

*IQR,* interquartile range. 
*CD4 T-lymphocyte data were missing for 18 of 186 patients (8, 4, and 6 patients in the three groups, respectively).*
population was 63.9% (95% CI, 55.8 to 70.4%); it was higher in patients from the cohort study (75.6%) but similar for the patients from the immediate and deferred ART group of the RCT (61.3% versus 58.6%). Thirty-five patients (4 from the cohort and 31 from the immediate and deferred ART group of the RCT (61.3%) were infected with an \( M. \) tuberculosis isolate that was sensitive to all five drugs (INH, RIF, SM, EMB, and PZA), 28 isolates were SM resistant only, 12 were INH resistant only, 40 were resistant to both SM and INH, and 8 were multidrug resistant. Of the MDR isolates, two were resistant to INH and RIF, five were resistant to INH, RIF, and SM, and a single isolate was resistant to INH, RIF, SM, and EMB. No isolates were resistant to PZA (Table 2).

Of 35 patients who received streptomycin, 18 isolates were sensitive to all drugs, 3 were resistant to SM, 3 were resistant to INH, 10 were resistant to INH and SM, and 1 was resistant to INH, SM, and RIF.

Kaplan-Meier survival curves for patients in five resistance categories (fully susceptible, SM mono-resistant, INH mono-resistant, INH and SM resistant, and MDR) and in predefined resistance pattern groups (group 1, fully susceptible or SM mono-resistant \([n = 126]\); group 2, INH resistant with or without SM resistance \([n = 52]\); group 3, multidrug resistant \([n = 8]\)) are displayed in Fig. 1a and b.

There was a significant difference between survival curves of patients with different antituberculosis drug resistance patterns (log rank test, \( P < 0.001 \)). Patients with fully susceptible or SM mono-resistant isolates had the highest survival rates, whereas those with MDR-TBM had the lowest survival, with all MDR-TBM cases dying within 41 days of study enrolment. For patients with INH-sensitive isolates, median survival was 192 days, with a 9-month mortality of 54.2% (95% CI, 44.1 to 62.5%). For patients with INH-resistant (non-MDR) isolates, median survival was 89 days, with a 9-month mortality of 81.5% (95% CI, 66.0 to 90.0%).

After adjusting for the effect of TB grade at presentation, baseline CD4 cell count, and cohort group in a multiple Cox regression analysis, the drug resistance pattern remained an independent predictor of mortality. The adjusted hazard ratio in comparison with fully susceptible or SM mono-resistant isolates was 5.21 (95% CI, 2.38 to 11.42; \( P < 0.0001 \)) for MDR patients and 1.78 (95% CI, 1.18 to 2.66; \( P = 0.005 \)) for patients with INH-resistant isolates (with or without SM resistance). The addition of SM resistance as an additional covariate was not significant (hazard ratio, 1.02; 95% CI, 0.66 to 1.59; \( P = 0.91 \)). There was also no evidence of an interaction between drug resistance status and TB grade (\( P = 0.29 \)), CD4 cell count (\( P = 0.63 \)), or study group (\( P = 0.61 \)). However, there was evidence of a time-dependent effect of INH resistance (with or without SM resistance) on survival, i.e., nonproportional hazards (\( P = 0.03 \)). Fitting separate INH resistance effects for the first 3 months (during the intensive TB treatment phase) and later gave adjusted hazard ratios (in comparison with fully susceptible or mono-resistant isolates) of 1.45 (95% CI, 0.87 to 2.40; \( P = 0.15 \)) for the first 3 months and 5.05 (95% CI, 2.23 to 11.44; \( P = 0.0001 \)) thereafter. Exploratory analyses showed that the model with a cutoff point at 3 months for modeling INH resistance led to a better fit (in terms of likelihood) than models with a cutoff point at other times.

Exclusion of 35 patients who received streptomycin did not substantially alter the adjusted hazard ratio for MDR patients (HR, 4.86; 95% CI, 2.11 to 11.22; \( P = 0.0002 \)) or INH-resistant patients (HR, 1.90; 95% CI, 1.20 to 3.00; \( P = 0.006 \)).

\( M. \) tuberculosis genotype data were available for 122 isolates. Of these, 18 (15%) were of the Indo-Oceanic lineage, 22 (18%) were of the Euro-American lineage, and 82 (67%) were of the East Asian/Beijing lineage (Table 3). Kaplan-Meier survival curves for the patients in the three lineages are displayed in Fig. 1c.

In the crude analysis (\( n = 122 \)), \( M. \) tuberculosis lineage had no significant effect on outcome (log rank test, \( P = 0.10 \)). Any impact of lineage on outcome is likely to be confounded by drug resistance phenotype. There were only two INH-resistant and two MDR-resistant Indo-Oceanic isolates (Table 3), and we therefore further analyzed the impact of lineage on outcome, including only patients infected with fully susceptible or SM mono-resistant strains (\( n = 83 \)) (Fig. 1d). In patients with susceptible isolates, there was a significant difference between the survival curves of patients with different lineages (log rank test, \( P = 0.01 \)). A Cox regression analysis adjusted for CD4 count, TB grade at presentation, and cohort group showed lower mortality in the East Asian/Beijing lineage compared to the Indo-Oceanic lineage strains, with an adjusted hazard ratio of 0.29 (95% CI, 0.14 to 0.61; \( P = 0.001 \)). There were no significant differences between East Asian/Beijing and Euro-American strains (HR, 0.64; 95% CI, 0.27 to 1.52; \( P = 0.31 \)) or between Euro-American versus Indo-Oceanic strains (HR, 0.45; 95% CI, 0.17 to 1.18; \( P = 0.11 \)).

Previous BCG vaccination (assessed by visible scar) was recorded in patients recruited to the RCT, and data were available for 74/81 (91%) of patients with \( M. \) tuberculosis genotype data. In these patients, we also analyzed the influence of previous BCG vaccination on the lineage of the infecting strain and duration of illness prior to presentation. There was a significant association between prior BCG vaccination and lineage (Fisher’s exact test, \( P = 0.01 \)). Patients with a prior BCG vaccination were less likely to be infected with the Beijing strain (Table 4).

There was no evidence for an association between lineage and duration of illness prior to presentation (Kruskal-Wallis test, \( P = 0.76 \)) or for duration of illness and BCG vaccination (Mann-Whitney test, \( P = 0.42 \)). There was also no evidence for an association between BCG vaccination and survival based on univariate analyses (\( P = 0.95 \)) or after adjustment for lineage and resistance category (\( P = 0.61 \)).

### DISCUSSION

Isoniazid resistance without concurrent rifampin resistance had a significant impact on outcome among HIV-associated TBM pa-

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**TABLE 2 Drug susceptibility profiles of \( M. \) tuberculosis isolates from CSF of 186 patients with HIV-associated TBM**

<table>
<thead>
<tr>
<th>Drug susceptibility profile</th>
<th>No. (%) in resistance group</th>
</tr>
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<tr>
<td>Fully susceptible</td>
<td>98 (52.7)</td>
</tr>
<tr>
<td>Streptomycin resistant</td>
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</tr>
<tr>
<td>Isoniazid resistant</td>
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</tr>
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<td>Isoniazid and streptomycin resistant</td>
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</tr>
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<td>Isoniazid, rifampin, and streptomycin resistant</td>
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</tr>
<tr>
<td>Isoniazid, rifampin, streptomycin, and pyrazinamide resistant</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>186</strong></td>
</tr>
</tbody>
</table>

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**DISCUSSION**

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**TABLE 3**

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tients treated with standard first-line antituberculosis therapy (adjusted HR, 1.78; 95% CI, 1.18 to 2.66; \(P = 0.005\)). Analyses modeling a time-varying effect of INH resistance and Kaplan-Meier survival curves (Fig. 1b) showed that the detrimental effect of INH resistance was most pronounced from month 3 onwards, when treatment with pyrazinamide and ethambutol was stopped and patients continued on isoniazid and rifampin only. This suggests it is possible that, in these patients effectively on RIF monotherapy during the continuation phase, a rifampin-resistant subpopulation was able to emerge once ethambutol and

**FIG 1** Kaplan-Meier survival curves of HIV-associated TBM patients infected with *M. tuberculosis*. (a) Curves for patients separated into five drug resistance categories; (b) curves for three drug resistance categories; (c) curves based on lineages of the *M. tuberculosis* strains for all patients; (d) *M. tuberculosis* lineage for patients infected with strains sensitive to all drugs or SM-monoresistant strains.

<table>
<thead>
<tr>
<th>M. tuberculosis lineage</th>
<th>No. (%) with drug susceptibility profile</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fully susceptible</td>
</tr>
<tr>
<td>Beijing</td>
<td>39 (47.6)</td>
</tr>
<tr>
<td>Euro-American</td>
<td>9 (40.9)</td>
</tr>
<tr>
<td>Indo-Oceanic</td>
<td>14 (77.8)</td>
</tr>
<tr>
<td>Total</td>
<td>62 (50.8)</td>
</tr>
</tbody>
</table>
pyrazinamide were discontinued, resulting in treatment failure and increased mortality. In this situation, extension of the duration of the intensive phase of treatment alone beyond 3 months may not be sufficient to achieve complete sterilization of the CSF, and it is likely that an alternative or additional bactericidal agent will be required. Of the currently available drug classes for TB, a fluoroquinolone is likely to represent the best option, and this is being explored in a treatment trial (trial registration number ISRCTN61649292) (8).

The HIV epidemic in Vietnam remains largely concentrated in high-risk groups, and the majority of HIV patients in this study were young male intravenous drug users. This may represent a bias for higher mortality than a more general HIV-TBM cohort. In accordance with previous studies, we found that MDR-TBM was uniformly fatal in this patient population when patients were treated with standard antituberculosis therapy. The rapid detection of drug resistance in TB cases is extremely difficult due to the paucibacillary nature of the disease. The widespread ongoing implementation of GeneXpertMTB/RIF (Cepheid) in high-TB-burden settings may enable rapid diagnosis of MDR-TBM, but data are not yet available on the accuracy of the technique in TB cases. Even if the diagnosis of drug-resistant TB were to be confirmed, there are no data from RCTs to guide clinical management (2, 5).

In pulmonary TB, recent meta-analyses have shown that outcomes are worse in patients infected with INH-resistant, RIF-sensitive *M. tuberculosis*, but treatment guidelines for INH-resistant pulmonary TB vary, and none are based on high-quality evidence from RCTs (10, 12). The WHO recommends adding ethambutol to the continuation phase in regions with a high prevalence of INH resistance (27), the American Thoracic Society recommends adding a fluoroquinolone “in extensive cavitary disease” (1), and the British Thoracic Society recommends an extended continuation phase of 7 months with EMB and RIF (13). These recommendations probably should not be extrapolated to the treatment of TBM, due to the need for high CSF penetration of bactericidal agents, and further studies are required to improve the early detection of drug-resistant bacteria in CSF and to determine the optimal treatment for both INH-resistant and MDR-TBM cases.

The multivariate regression model suggests the lineage of the infecting *M. tuberculosis* strain influenced the outcome for patients infected with fully susceptible strains. Intriguingly, patients infected with the modern Beijing strains had a lower mortality risk than those with the ancient Indo-Oceanic strains. A previous study of the impact of *M. tuberculosis* lineage on mortality for 160 HIV-uninfected TB patients showed that a higher proportion of patients infected with Beijing lineage strains were dead or severely disabled at 9 months, but this difference did not reach significance (19). We previously showed an association between Beijing genotype and HIV-associated TBM in this setting (4), but the data presented here show that HIV patients infected with a Beijing lineage did not have a higher mortality rate. The higher event rate for mortality among HIV-associated TBM may have increased the ability to detect a difference between the lineages, or the difference may have been due to variable pathogenesis with HIV coinfection. The modern Beijing and Euro-American lineages have proinflammatory profiles and show an increased propensity to disseminate in a mouse model, compared to the ancient Indo-Oceanic strains (9). There is increasing evidence of differences in virulence between the major lineages of *M. tuberculosis* in different host populations (3, 7). The mechanism responsible for these differences remains unclear but may be due to differential immune modulation (18); it is possible that the proinflammatory effect, while detrimental in immunocompetent patients, conversely reduces the severity of TB in severely immunocompromised patients.

We have also shown an association between infection with a Euro-American strain and vaccination, with HIV-infected TB patients who are BCG vaccinated less likely to be infected with a Beijing strain of *M. tuberculosis*. This is an unexpected finding, as it has been previously hypothesized that the success of the Beijing strain is attributable to a lower protective efficacy of BCG against Beijing lineage strains, although the evidence to support this theory remains weak (14). The patients in this study were severely immunosuppressed, which may alter the protective dynamics of the immune response to BCG. An improved understanding of the differential immune evasion mechanisms of *M. tuberculosis* lineages is vital to the development of a globally effective vaccine (7).

In conclusion, this study demonstrates that isoniazid resistance, multidrug resistance, and bacterial lineage are important determinants of outcome for TB. Methods to improve the rapid diagnosis of drug-resistant TBM and clinical trials to determine optimal antimicrobial treatment strategies are urgently required.

ACKNOWLEDGMENTS

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We report no conflicts of interest.

REFERENCES


